REC'D 15 DEC 2004
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P61263PC00	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/NL 03/00601	International filing date *(day/month/year)* 28.08.2003	Priority date *(day/month/year)* 29.08.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/107		
Applicant OCTOPLUS SCIENCES B.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.03.2004	13.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Luangkhot, N Telephone No. +49 89 2399-7857

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL 03/00601

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-33 as originally filed

Claims, Numbers

1-36 filed with telefax on 23.11.2004

Drawings, Sheets

1/8-8/8 as originally filed

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-36
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-36
Industrial applicability (IA)	Yes:	Claims	1-36
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item I

Basis of the report

1) The documents cited in the International Search Report (ISR) were numbered respectively from D1-D6; this numbering results from the citation order in the ISR and will be used for the procedure. Unless not specified, the cited passages of each document in the ISR will be considered.

2) The formulations in independent claims 1 and 17 such as "characterized in that [...] the polymers [...] are capable of forming an aqueous two-phase system" do not delimit the scope of the protection to be sought and are rather to be construed as an attempt to define the invention by a **result to be achieved**, in particular they only amount to claiming the underlying technical problem.

   Such definitions are only allowable under the conditions elaborated in the Guidelines C-III, 4.7. In this instance, however, **such formulations are not allowable because it appears possible to define the subject-matter in more concrete terms, viz. in terms of how the effect is to be achieved by incorporating for example the chemical structures or generic names or hydrophilic property of the polymers used,...**

3) New amended claims 1-36 are allowable according to Article 34(2)(b) PCT because a support was found in the description and no subject-matter which extends beyond the content of the application as filed was introduced.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

4) Novelty and inventive step according to Art. 33(2) and 33(3) PCT

4a) The subject-matter of independent claim 17 and its dependent claims 18-34 is novel because none of the cited documents describes a block copolymer A-B, characterized in that the polymers A and B are capable of forming an aqueous two-phase system.

4b) For the same reason the subject-matter of independent claim 1 and its dependent claims 2-16,35-36 is novel because none of the cited prior art documents describes a drug carrier system, or a pharmaceutical composition comprising the said block copolymer A-B, characterized in that the polymers A and B are capable of forming an aqueous two-phase system.

4c) However the subject-matter of independent claims 1 or 17 does not involve an inventive step because neither claim 1 nor claim 17 contain any technical feature that contributes to solve the problem, which is to provide a block copolymer A-B capable of forming an aqueous two-phase system.
Put in other way claims 1 and 17 are construed as an attempt to define the invention by a result to be achieved, in particular they only amount **to claiming the underlying technical problem**.

The problem to be solved can be seen as providing a block copolymer A-B capable of forming an aqueous two-phase system.

The solutions suggested in the dependent claims are so broadly claimed that it is highly doubtful that the problem is solved over the whole scope determined by the features of the dependent claims.

Put in other words, it is difficult to believe that any block co-polymer A-B, **even if A and B are both hydrophilic**, is capable of forming an aqueous two-phase system and thus can be used as an agent for making a drug carrier system (claim 1), or as a stabilizer of an aqueous two-phase system (claim 27), or as a micelle forming agent in an aqueous system (claim 28), or as a component of an aqueous composition (claims 29-31).

The applicant should restrict the claims to a reasonable generalisation or provide evidence that the problem is solved for any possible combination of copolymer as described in the dependent claims, not only for the copolymer Dex-mPEG (combination of claims 11 and 12, or claims 23 and 24) as already exemplified in the description.

Failure to do so would lead to maintain the inventive step objection since the problem is not solved.

For the regional phase:

5) Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and

for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application.

6) Contrary to the requirements of Rule 5.1(a)(ii) PCT, it seems that the relevant background art disclosed in the document D1 is not mentioned in the description, nor are this document identified therein.

7) The attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT). Preferably these indications should be submitted in handwritten form on a copy of the relevant parts of the application as filed.

Claims

1. A drug carrier system comprising a plurality of colloidal particles having a micellar structure with core and a shell, said particles comprising copolymer molecules, which copolymer comprises at least one A block and at least one B block different from the at least one A block, wherein the at least one A block consists of a polymer unit of a first set of monomers and the at least one B block consists of a second set of monomers, characterized in that the first set of monomers and the second set of monomers are selected in such a way that polymers only consisting of monomers of the first set and polymers only consisting of monomers of the second set are capable of forming an aqueous two-phase system, and in that the A blocks in particles form the core and the B blocks in the particles form the shell.

2. The drug carrier system of claim 1, ~~wherein said particles comprises a micellar structure~~ comprising the plurality of colloidal particles, which colloidal particles are cross linked.

3. The drug carrier system of claim 1 or 2, having intermolecular crosslinks between at least some of the A blocks in the same particle.

4. The drug carrier system of claim 1, 2 or 3, having intermolecular crosslinks between at least some of the B blocks in the same particle.

5. The drug carrier system of any one of the preceding claims, further comprising a polymer consisting of monomers of the first set.

6. The drug carrier system of claim 5, having intermolecular crosslinks between at least some of the A blocks and at least some of the

chains of the polymer consisting of monomers of the first set in the same particle.

7. The drug carrier system according to any one of the preceding claims, wherein the A block has a biodegradable backbone.

8. The drug carrier system according to claim 3 or claim 6, having biodegradable spacers between block A and at least some of the intermolecular crosslinks.

9. The drug carrier system of claim 8, wherein the biodegradable spacers comprise a hydrolysable ester bond, a hydrolysable amide bond, or a hydrolysable carbonate bond.

10. The drug carrier system according to any one of the preceding claims, wherein the A block consists of a polymer unit of saccharides or derivatives thereof.

11. The drug carrier system according to claim 10, wherein the saccharide is a dextran, optionally modified with an acrylic, a methacrylic or a hydroxyethylmethacrylic group.

12. The drug carrier system according to any one of the preceding claims, wherein the B block consists of a polymer unit of ethylene glycols.

13. The drug carrier system according to any one of the preceding claims, wherein the colloidal particles are substantially insoluble in an aqueous liquid at physiological conditions.

14. The drug carrier system according to any one of the preceding claims, wherein the colloidal particles have a mean particle size of between 5 nm and 50 µm.

15. The drug carrier system according to any one of the preceding claims, further comprising an active ingredient and preferably a pharmaceutically active ingredient.

16. A pharmaceutical composition comprising the colloidal drug carrier system according to any one of the preceding claims.

17. A block copolymer comprising at least one A block and at least one B block different from the at least one A block, wherein the at least one A block consists of a polymer unit of a first set of monomers and the at least one B block consists of a second set of monomers, characterized in that the first set of monomers and the second set of monomers are selected in such a way that polymers only consisting of monomers of the first set and polymers only consisting of monomers of the second set are capable of forming an aqueous two-phase system, and wherein the at least one A block comprises one or more crosslinkable groups.

18. The copolymer according to claim 16, having the structure A-B or A-B-A.

19. The copolymer of claim 17 or 18, wherein the A block possesses a biodegradable backbone.

20. The copolymer according to any one of claims 17-19, wherein a biodegradable spacer is present between the A block and at least some of the crosslinkable groups.

21. The copolymer of claim 20, wherein the biodegradable spacer comprises a hydrolysable ester bond, a hydrolysable amide bond, or a hydrolysable carbonate bond.

22. The copolymer according to any one of claims 17-21, wherein the A block consists of a block selected from the group consisting of native polysaccharides, modified polysaccharides, polyalkylene oxides, polyalkylene glycols, polyvinyl alcohol, polyvinylpyrrolidone, and proteins.

23. The copolymer of claim 22, wherein A block is comprised of dextran units, optionally modified with acrylic, methacrylic or hydroxyethylmethacrylic groups.

24. The copolymer according to any one of the claims 17-23, wherein the B block is a polyethylene glycol block.

25. The copolymer according to any one of the claims 17-24, further comprising at least one block C which is different from the A block and the B block.

26. The copolymer according to any one of the claims 17-25, wherein the B block further comprises a ligand, such as a target-recognizing peptide, protein, antibody, or carbohydrate.

27. Use of the copolymer according to any one of claims 17-26 as a stabilizer of an aqueous two-phase system.

28. Use of the copolymer according to any one of claims 17-27 as a micelle forming agent in an aqueous system.

29. An aqueous composition comprising the copolymer according to any one of claims 17-26.

30. The composition of claim 28 wherein polymers consisting of monomers of the first set and polymers consisting of monomers of the second set are present in an amount effecting a phase separation between a first aqueous phase rich in polymers consisting of monomers of the first set and a second aqueous phase rich in polymers consisting of monomers of the second set.

31. The composition of claim 30, wherein the second aqueous phase forms the continuous phase of the two-phase system.

32. Method for the preparation of a drug carrier system comprising a plurality of colloidal particles, said method comprising the steps of:

(a) preparing an aqueous colloidal solution comprising micelles, said micelles being comprised of a block copolymer according to any one of claims 16-25; and

(b) crosslinking at least some of the crosslinkable groups; wherein step (b) is carried out after step (a).

33. The method of claim 32, wherein step (b) is carried out in the presence of an active substance.

34. Method for the preparation of a drug carrier system comprising a plurality of colloidal particles, said method comprising the steps of:

(a) preparing an aqueous two-phase system, said system comprising:

(aa) block copolymer according to any one of claims 16-25;

(bb) polymer consisting of monomers of the first set;

(cc) polymer consisting of monomers of the second set; and

(dd) water;

wherein the relative amounts of polymer (bb), polymer (cc) and water are selected to induce a phase separation;

(b) crosslinking at least some of the crosslinkable groups;

wherein step (b) is carried out after step (a).

35. The method of any one of claims 32-34, wherein the aqueous two-phase system comprises a further block copolymer as defined in claim 1.

36. The method of claim 35 wherein at least a part of the B blocks of the block copolymers comprises a target recognizing ligand, such as an antibody, peptide, protein, or carbohydrate.